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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/448,613	MCCRAY JR. ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-70* is/are pending in the application.

4a) Of the above claim(s) *13-25,57-59,61 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,26-56,60 and 63-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A response to restriction requirement was received and entered as Paper No. 9 on 9/4/01. The Examiner noticed that several claims were omitted from the restriction requirement and set forth a new requirement in a telephone interview with Stephen Highlander on 11/14/01. A provisional election was made without traverse to prosecute claims 1-37, 48-67, and 70, drawn to methods of treating disease, and the following species were elected: retrovirus, membrane channel, cystic fibrosis, and the combination of a hypotonic solution and a chelator. After further consideration, all claims have been rejoined into the elected group, and will be examined to the extent that they are defined by the elected group and correspond to the elected species. The relationship between the elected species and the claims is as follows:

Species	Reading On	Generic
Retrovirus	1-70	1-30, 32-41, 43-46, 47-51, 53-66, and 67-70
Membrane Channel	1-70	1-28, 29-63, and 65-70
Cystic Fibrosis	1-56, 60, and 63-70	1-32, 34-56, 60, and 63-70
Hypotonic sol. + chelator	1-12, 26- 70	1-12 and 26-67

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after

the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Claims 13-25, 57-59, 61, and 62, are withdrawn from further consideration as being drawn to non-elected species. Claims 1-12, 26-56, 60, and 63-70 are under consideration in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1-12, 26-56, 60, and 63-70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant invention is directed to improving the efficiency of gene transfer to epithelial cells by increasing the transepithelial permeability of the epithelial sheet. Recent publications, as well as the specification, indicate that receptors for adenovirus, adeno-associated virus, and retroviruses tend to be sequestered on the basolateral surface of the lung epithelial cells, and are therefore not available to bind viruses delivered via the lumen of the lung. The essence of the instant invention is two provide access to these receptors by either allowing viruses to penetrate the epithelium and associate with its basolateral surface, or by causing redistribution of the

receptors to the apical surface of the epithelium, which is exposed to the lumen of the lung.

Claims 1-9, and 26-37 are drawn to methods of increasing the susceptibility of epithelial cells to retroviral infection comprising increasing the transepithelial permeability of epithelial tissue comprising the cells through the use of a hypotonic solution and EGTA. Claims 38, 40-43, and 45-48 are drawn to compositions comprising a hypotonic solution and EGTA and a cell proliferative factor. Claims 48 and 49 are drawn to methods of redistributing viral receptors on epithelial cells of an epithelial tissue comprising increasing the transepithelial permeability of the epithelial tissue through the use of a hypotonic solution and EGTA. Claims 50- 52 are drawn to methods of expressing a membrane channel in cells of an epithelial tissue comprising the step increasing the transepithelial permeability of the epithelial tissue through the use of a hypotonic solution and EGTA. Claims 53-56, 60, and 63-67 are drawn to methods of treating cystic fibrosis (CF) comprising the step of increasing the transepithelial permeability of the epithelial tissue through the use of a hypotonic solution and EGTA. Claims 68 and 69 are drawn to compositions comprising hypotonic solution and EGTA. Claim 70 is drawn to a method increasing the susceptibility of epithelial cells to retroviral infection comprising delivering to said cells a packaged retroviral vector and EGTA in a hypotonic solution. The elected invention relates to the delivery of therapeutic genes to diseased tissues *in vivo*. See page 2, lines 11 and 12, page 13, lines 1-10. The specification discloses no use for the claimed methods and compositions other than the treatment of disease, and the only readily apparent use other than disease treatment is in the process of developing such treatments. Thus, in order to enable the

elected methods and compositions, the specification must teach how to treat CF by administration to epithelial cells *in vivo* of a retroviral vector encoding a membrane channel, wherein the permeability of the epithelial tissue is increased by treatment with a hypotonic solution and EGTA.

At the time the invention was made, successful implementation of gene therapy protocols in general was not routinely obtainable by those skilled in the art. This is reflected by three recently published reviews. Orkin (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995) teaches that "significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host" (page 1, item 3). Orkin teaches that problems exist in delivering nucleic acid sequences to the appropriate target cell or tissue and achieving the appropriate level of expression within that cell or tissue (page 9). Verma et al (Nature 389: 239-242, 1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30).

At the time of the invention, the treatment of CF through the administration of genes encoding membrane channels was not routinely practiced with success by those of skill in the art due to poor gene transfer efficiency and expression. In addition, one of the most important barriers to gene therapy of CF is the lack of information regarding the appropriate target cells for gene delivery. Rosenfeld and Collins (Chest 109:241-252, 1996) teach that it is unclear exactly which cells should receive [gene therapy]", stating that "[t]he difficulty in determining which cells to target relates to an inability to draw parallels between the normal pattern of CFTR expression and the development of CF in lung disease. In normal individuals, the surface epithelium of small airways expresses very low levels of CFTR, while the submucosal glands found exclusively in large airways express much higher levels. In contrast, in CF, the most important pathologic consequences occur first in the small airways with alveolar damage as a consequence. Little if any clinically significant disease ever occurs where the submucosal glands are found." Boucher (TIG 12(3): 81-84, 1996) notes that this issue is relevant to strategies for vector delivery because while the superficial epithelium of airways can be reached by lumenal vector delivery, the submucosal glands may require systemic administration. See page 1 of reprint, column 2, last sentence of first full paragraph. Rosenecker (Eur. J. Med. 23(3): 149-156, 3/1998) teaches that "[t]opical administration of gene transfer vectors to airways is impeded by surface fluid, mucus plugging the airway lumen, and the ciliated apical surface of epithelial cells" and that the submucosal glands are inaccessible for topically applied formulations. Thus systemic delivery via the blood stream is indicated. See page 152, column 2, lines 1-15 of

second full paragraph. The instant specification fails to address systemic delivery in the treatment of CF, focusing instead on lumenal delivery. So, if it turns out that transfection of submucosal glands is required for the treatment of CF, then the specification has failed to provide an enabling disclosure because it provides insufficient guidance as to how to deliver retroviral vectors to cells of the submucosal glands. Further evidence of the unpredictability of CF gene therapy comes from Wilson (J. Clin. Invest. 96(2547-2554, 12/1995) who teaches that the program of expression of CFTR in the lung is extraordinarily complicated, and that the effect of omitting submucosal glands from treatment is unknown. Wilson also notes that vector targeting and gene expression are currently nonspecific, resulting in ectopic and unregulated expression of CFTR. See page 2548, first full paragraph.

Because it is unknown what cell types need to be transfected in order to treat CF, it is also unclear how many cells must be transfected and what level of gene expression is required in order to achieve therapy. This is readily apparent from a review of the literature both before and after the filing date of the instant application. See e.g. Rosenfeld and Collins (1996, first full paragraph of column 1 on page 243); Boucher (TIG 12(3): 81-84, 1996, page 81, paragraph bridging columns 2 and 3); Alton and Geddes (J. R. Soc. Med 90 Suppl 31: 43-46 1997); Davies (Mol. Med Today 4(7): 292-299, 7/1998, page 294, column 2, lines 20-28); Boucher (J. Clin. Invest. 103(4): 441-445 2/1999); and Flotte (Chest 120: 124S-131S, 2001, page 124S, column 2 second full paragraph). The level of expression required for therapy is also unknown because the relationship between abnormal ion transport and pathophysiology of CF is incompletely

understood. Briefly, the molecular problem responsible for CF is a defect in a chloride ion transporter known as CFTR. One hypothetical explanation for the progress of the disease depends on a failure to transport chloride ions, leading to abnormal absorption of sodium ions by the epithelium. This leads to dehydration and thickening of the mucus in the lungs, which in turn leads to a variety of pathophysiological outcomes including inflammation, repeated infections, and decreasing pulmonary function. Alternatively, the defect in CFTR could somehow affect the actual composition of mucus in the lung, resulting in the recognized pathologies. See Wilson (1995) paragraph bridging pages 2547 and 2548. Thus a primary focus of treatment is the restoration of chloride ion transport. Boucher (1999) teaches that it is likely that the percentage of epithelial cells requiring functional correction to restore normal chloride ion transfer *in vivo* may well exceed 10%, and advises that the simplest strategy to assure efficacy is to mimic the normal pattern of *in vivo* expression by achieving gene expression in 100% of lung epithelial cells. See paragraph bridging pages 441 and 442, page 442 column 1, lines 25-30, and 42- 45. Boucher concludes that a one or two order of magnitude increase in *in vivo* gene transfer efficiency, above that observed in clinical trials, will be required for therapeutic relevance in CF treatment. See page 444, column 2, first sentence of second full paragraph. Clinical studies have shown success in partially correcting chloride ion transport, however Alton and Geddes (1997) teach that it is unknown whether the chloride or sodium defect associated with CF is the more important error to correct, and that the degree of correction needed for clinical benefit of these defects is unknown. See page 45, lines 7-10 of first full paragraph. Furthermore, Davies (1998)

teaches that if normalization of sodium ion transport is required for therapeutic effect, then the levels of gene transfer observed to date will be inadequate because correction of sodium ion transport has not been achieved in the majority of preclinical and clinical studies. See page 294, column 2, lines 22-28. Rosenfeld (1996) indicates that although restoration of chloride conductance in monolayer cells is achieved by transfection of 5-7% of the cells, normalization of sodium ion reabsorption will require transfection of a much higher percentage of cells. See page 243, column 1, lines 15-18. For these reasons it was apparent at the time of the invention that the practice of gene therapy of CF was highly unpredictable. Shortly after the application was filed, Boucher (1999) summarized the state of the art by stating that "despite an impressive amount of research in this area, there is little evidence to suggest that an effective gene transfer approach for the treatment of CF lung disease is imminent."

Against this background, the specification teaches working examples in which normal rabbit lungs were treated with EGTA *in vivo* in order to either permeabilize the epithelium, or cause receptor redistribution, prior to infection with retroviral vectors. From 2.5% to 4.8% percent of rabbit lung epithelial cells were transfected. See page 73, lines 19-26, and page 74, lines 10-12, and 25-27. However, the teachings of the those of skill in the art at the time of the invention indicate that transfection of at least 6-10% of epithelial cells would be required in order to restore normal chloride ion transport *in vivo*. See Johnson et al (of record C40). However, as noted by Boucher (1999), this estimate is based on *in vitro* assays using monolayer epithelial cells which were highly connected by gap junctions. This allows chloride ions from over-

corrected cells to diffuse to uncorrected cells. Boucher indicates that it is likely that the number of gap junctions *in vivo* is less than that in the *in vitro* monolayer model, so the minimum number of cells which must be transfected *in vivo* may well exceed 10%. See page 442, column 1, lines 5-29. As noted above, this issue is further complicated by the fact that it is not known what level, if any, of chloride ion transport will result in correction of the sodium ion transport defect, which may be more important in the pathology of the disease. See Alton and Geddes (1997) and Davies (1998), above. It is further noted that the rabbits used in these assays were normal, see page 73, line 23, and thus did not suffer from the accumulation of mucus associated with the CF in humans, which impedes vector access to the epithelium according to Rosenecker (1998, see page 152, column 2, lines 1-15 of second full paragraph). See also Davies (1998) page 292, column 2, lines 7-9 of first paragraph. For this reason, one of skill in the art could not reproduce in a CF patient the level of gene transfer observed in the rabbit model of the working example. Thus, even if one accepts that 6-10% transfection of epithelial cells is sufficient for treatment of CF, the instant specification has failed to teach how to achieve this level of transfection in a CF patient.

It is also noted that the scope of membrane channels which may be used in the invention is not limited to CFTR but encompasses all membrane channels. Even if the specification taught how to use the CFTR membrane channel to treat CF, which it does not, the specification does not teach how to use any other membrane channel in the treatment of CF. The CFTR polypeptide is a chloride ion transporter which appears to be regulated by phosphorylation. See Rosenecker

(1998, page 149, column 2, lines 11-14). One of skill in the art would not expect that a membrane channel designed for transport of other ions could be used to treat the disease, and the specification offers no guidance in this regard. For example, the specification fails to teach how to use the F_OF_1-ATPase/synthase, which comprises a membrane channel for hydrogen ions, in the treatment of CF. Furthermore, the specification fails to teach any example of a membrane channel that responds to the same regulatory signals as CFTR and in the same ways. Thus the specification has failed to teach how to restore appropriate cellular function using membrane channels other than CFTR, and one of skill in the art could not treat CF with such channels without undue experimentation.

In summary, while the specification teaches how to improve retrovirus infection of epithelial cells *in vivo*, it fails to teach how to use the claimed methods and compositions for the purpose intended by the specification, *i.e.* gene therapy of CF. The specification fails to add to the teachings of the prior art with respect to the identification of the type of cells which must be transfected, the number of cells which must be transfected, or the level of expression which is required in order to treat CF. It fails to teach whether or not CF can be treated by restoring only chloride ion transport, or if restoration of the sodium ion defect is required. It also fails to teach how to achieve correction of the sodium ion defect. Finally it fails to teach how to transfect the minimum number of cells which the prior art suggests will be required to treat CF. Furthermore, gene therapy of CF is highly unpredictable because the prior art had established that both the target cells for treatment, and the nature of the defect which required correction were unknown.

Because the prior art teaches that it is not known which cells must be transfected with CFTR expression vectors in order to treat CF, how many of these cells must be transfected, or what level of expression must be obtained to effect treatment; because the instant invention provides transfection of a lower percentage of cells than the minimum which is deemed necessary by those of skill in the art to correct the CF chloride ion transport defect; because it is unknown if correction of the chloride ion transport defect will result in any therapeutic effect; and because the specification fails to provide the requisite teachings missing from the prior art, one of skill in the art would have to perform undue experimentation in order to use the invention as intended.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12, 32, 33, 48-52, and 68-70are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-12 and 70 are indefinite because the method steps are not concordant with the purpose set forth in the preamble. The claim recites no step in which the susceptibility to viral infection is increased.

Claim 8 is indefinite because it fails to further limit claim 7. More specifically, the between the "proliferative factor" of claim 7, and the "growth factor" of claim 8 is not clear, thus it is not clear how claim 8 further limits claim 7. Neither the specification nor the claims provide a definition for the terms "proliferative factor" and "growth factor", thus one of skill in the art is not apprised of the metes and bounds of the claim.

Claims 32 and 33 are indefinite because they recite the term "diseased", which is a relative term. The term "diseased" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Specifically, the parameter of "tissue" is rendered indefinite by the use of the term "diseased". For example, although claim 33 recites a disease, cystic fibrosis, it is unclear what tissues correspond to diseased tissues. All tissues in a CF patient lack CFTR function, but are all tissues diseased?

Similarly, claims 68-70 are indefinite because they require a hypotonic solution, but they provide no standard of comparison which can be used to determine whether or not a given solution is hyper-, hypo-, or isotonic.

Claims 48 and 49 are indefinite because the method steps are not concordant with the purpose set forth in the preamble. The claims recite no step in which the viral receptors are redistributed.

Claims 50-52 are indefinite because the method steps are not concordant with the purpose set forth in the preamble. The claims recite no step in which the polypeptide is expressed.

Claim 69 is indefinite because it recites "a package viral vector". This is not a term of art, and it is not defined in the specification. Substitution of the word "packaged" for the word "package" is suggested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 6-8, 26-31, and 48-52 are rejected under 35 U.S.C. 102(b) as being anticipated by Halbert et al (Human Gene Therapy 7(15): 1871-18881, 10/1996), as evidenced by Puchelle (Acta Oto-Rhino-Laryng. Belg. 54 (3): 263-270, 2000).

Halbert teaches a method of increasing the susceptibility to retroviral infection of rabbit tracheal cells *in vivo*. Rabbit tracheas were abraded by brushing, resulting in a wound which necessarily increases transepithelial permeability. Replication defective retroviral vectors were delivered to the sites of the wounds. Infection of wounded rabbit tracheas was increased relative to that observed in unwounded tracheas. The retroviruses expressed the enzyme human placental alkaline phosphatase. See last sentence of abstract; page 1872, column 2, lines 12-20; Fig. 1 on

page 1873; page 1874, column 2, second full paragraph, and lines 1-4 of next paragraph and Fig. 4 on page 1878. See also paragraph bridging columns 1 and 2 on page 1878.; paragraph bridging pages 1874 and 1875.

Claims 7 and 8 are included in this rejection because, although Halbert increases cellular proliferation by wounding rather than by direct application of a proliferative factor, the act of wounding cases the subsequent release of proliferative factors from the wounded tissue. Puchelle teaches that wounded airway epithelium is regenerated in a process involving growth factors. Thus damaging airway epithelial cells results in the subsequent contacting of these cells by growth factors. In other words, the step of contacting epithelial cells with growth factors is inherent in the method steps taught by Halbert.

Claim 29 is included in the rejection because it recites "enzymes" as a species of polypeptide which can be expressed by the retrovirus, and Halbert teaches the enzyme human placental alkaline phosphatase.

Thus Halbert anticipates the claims.

It is noted that even though Halbert is not considered to be enabling for therapeutic methods, the method steps of Halbert still read on the rejected claims. Even though the specification discloses no use for the claimed method other than gene therapy, the rejected claims do not recite a therapeutic outcome, thus the PTO is obligated to set forth the rejection because the prior art teaches the same methods steps as the claims.

Claims 38 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by either one of Mallea et al (FEBS Lett. 218(1): 143-147) or Yamaguchi et al (Peptides 16(8): 1483-1488, 1995).

Mallea teaches a liquid composition comprising tissue culture medium, EGTA and epidermal growth factor. See lines 5 and 6 of abstract. Absent evidence to the contrary, the composition is suitable for either aerosol or topical application.

Thus Mallea anticipates the claims.

Yamaguchi teaches a liquid composition comprising tissue culture medium, EGTA and transforming growth factor beta. See lines 11 and 12 of abstract. Absent evidence to the contrary, the composition is suitable for either aerosol or topical application.

Claims 68-70 are rejected under 35 U.S.C. 102(b) as being anticipated by Wunderlich et al (Arch. Vir. (73(2): 171-183, 1982).

Wunderlich teaches a composition comprising a EGTA and retroviral vectors. Wunderlich is silent as to whether the composition is hypotonic. However, because "hypotonic" is a relative term, and neither the claim nor the specification sets forth a standard for comparison, the solution of Wunderlich can be considered to be hypotonic relative to any solution comprising a greater concentration of salt.

Thus Wunderlich anticipates the claims.

It is noted that the compositions of Mallea, Yamaguchi, and Wunderlich are not enabled for use in gene therapy.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Patsy Zimmerman whose telephone number is 703-308-8338.

Richard Schnizer, Ph.D.